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Synthesis of highly functionalised 4-substituted 1, 3-diphenylpyrazole derivatives via reductive amination protocol using $ZnCl_2$ and $NaCNBH_3$

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ABSTRACT

A series of highly functionalised 4-substituted 1,3-diphenylpyrazoles derivatives were synthesised by the reaction of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde with variously substituted amines following a reductive amination protocol using $ZnCl_2$ and $NaCNBH_3$.

Keywords: 1,3-diphenylpyrazoles, Vilsmeyer Reaction, Reductive amination.

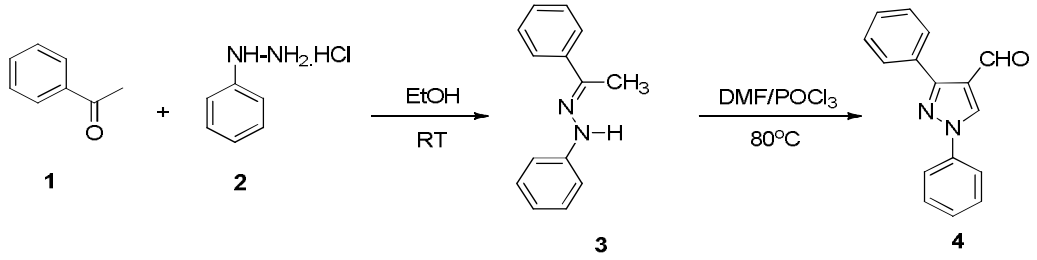
INTRODUCTION

Pyrazole and its derivatives, a well known class of nitrogen containing heterocyclic compounds, occupy a very important position in medicinal and pesticide chemistry exhibiting antimicrobial[1], anti-cancer[2], anti-inflammatory[3], anti-depressant[4], anti-convulsant[5], antihyperglycemic[6], antipyretic[7], anti bacterial[8], antifungal activities [9], CNS regulants[10] and selective enzyme inhibitory activities[11]. It has been found that these compounds have hypoglycemic activity, and are also known as inhibitors and deactivators of liver alcohol dehydrogenase and oxidoreductases[12]. Further, these compounds shown to possess appreciable anti-hypertensive activity in-vivo[13] and also exhibit properties such as cannabinoid hCB1 and hCB2 receptor, inhibitors of p38 Kinase, CB1 receptor antagonists[14,15]. The 4-substituted 1,3-pyrazoles were also found to possess anti-parasitic [16] and anti-proliferative activities[17].

Owing to the potential biological activities of the 4-functionalised 1,3-diphenylpyrazoles analogues cited in the literature and also due to our ongoing programme directed towards the synthesis diversely functionalised 1,3-diphenylpyrazoles we herein report our efforts in the directions to synthesise the said compounds.

MATERIALS AND METHODS

The required pyrazole-4-carboxaldehyde was synthesised via a two step sequence following literature procedure[18].



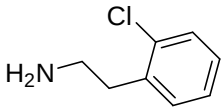
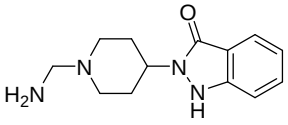
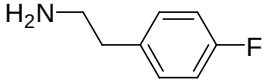
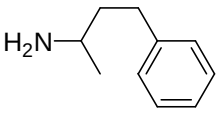
Scheme-1

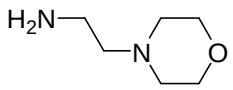
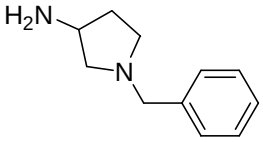
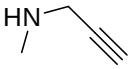
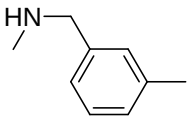
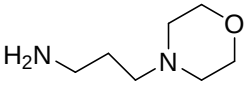
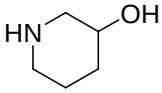
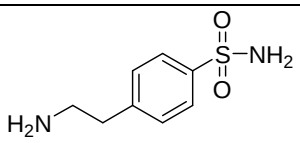
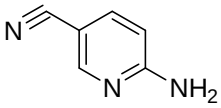
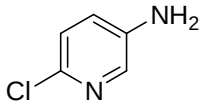
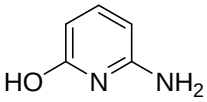
The 1,3-diphenyl-1H-pyrazole-4-carbaldehyde **4**, thus obtained was then treated with variously substituted amines both alkyl and aryl under reductive amination conditions using $ZnCl_2$ and $NaCNBH_3$ in presence of ethanol and trace amounts of acetic acid to afford the corresponding substituted aminopyrazoles **5a-n** (**Scheme-2**). Out of 15 amines used in the reactions, 5b, 5c and 5h gives the yield morathan 90% where as compounds 5i, 5j and 5l gave the low yield compared to other amines.

Scheme-2

The physical and chemical properties of the functionalised 4-substituted 1, 3-diphenylpyrazole derivatives **5a-5n** are depicted in **Table-1.**

Table-1: Synthesis of novel 4-substituted 1, 3-diphenylpyrazoles 5a-n.

Sr. No.	Reagent Used	Amine Used	Product	Yield	M.P. (°C)
1.	**4**		**5a**	**86**	135
2.	**4**		**5b**	**91**	184
3.	**4**		**5c**	**95**	148
5.	**4**		**5d**	**85**	153

6.	**4**		**5e**	**78**	138
7.	**4**		**5f**	**80**	144
8.	**4**		**5g**	**76**	134
9.	**4**		**5h**	**92**	161
10.	**4**		**5i**	**75**	136
11.	**4**		**5j**	**65**	110
12.	**4**		**5k**	**71**	166
13.	**4**		**5l**	**65**	142
14.	**4**		**5m**	**72**	156
15.	**4**		**5n**	**68**	128

Experimental:

Melting points were obtained on a MP apparatus SP 62 and are un-corrected. Infrared spectra were recorded on a FT-IR, Perkin-Elmer Spectrum-I spectrometer and the NMR spectra on a Bruker at 400 M Hz instrument-using TMS as internal standard.

Preparation of N-phenyl-N'-(1-phenylethylidene)-hydrazine (3)[16]: Phenyl hydrazine hydrochloride (2g, 13.8mmol, 1.0 eq) was added to a solution of acetophenone (1.8g, 15.2 mmol, 1.1 eq) in 50 ml of ethanol at 0 ^{o}C followed by the slow addition of glacial acetic acid (1.5ml). The reaction mixture was then refluxed for 2 h (tlc) and cooled to room temperature, when the product precipitated out of the reaction mixture. The product was filtered, washed with cold ethanol (2 x 10 ml) and dried under vacuum to obtain pure acetophenone phenylhydrazone as a yellow colored solid (2.8g, 90%). M.P.104 ^{o}C.

Synthesis of 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde (4) [16]: Phosphoryl chloride (1.03 ml, 11.4 mmol, 1.2 eq) was added to N, N-dimethylformamide (0.84 ml, 11.4 mmole, 1.2 eq) at 0^{o}C and the mixture stirred at the same temperature for 1h. This mixture was then slowly added to a solution of acetophenone phenylhydrazone **3** (2 g, 9.5 mmol, 1.0 eq) in DMF (5ml) and the reaction mixture was allowed to stir for 10 min at the same temperature and then heated to 70 ^{o}C for 3h (tlc). The reaction mixture was then cooled to room temperature and basified with cold and saturated aqueous potassium carbonate solution, when a brown colored solid precipitated out. The precipitate was filtered, washed with cold water (2 x 20 ml) to obtain the crude product as a brown solid. The crude products was purified by silica gel column chromatography using a mixture of hexane and ethyl acetate (92:8) to obtain pure product **4** as an off-white solid (2.17g 92%). M.P.: 146. ^{1}H-NMR (DMSO-d6): 9.99 (s, 1H), 9.34 (s, 1H), 7.42-7.60 (m, 6H), 7.92-8.01 (m, 4H); MASS: 248.09(M^{+}).

General procedure for the synthesis of substituted pyrazoles 5a-5n: A suspension of $ZnCl_2$ (0.8 eq) and $NaCNBH_3$ (1.2 eq) in methanol (10 ml) was stirred for 2 h at room temperature and to this was added a mixture of compound-**2** (1.0 eq) and the respective amine (1.0 eq) in dichloromethane (10 ml). The reaction mixture was then stirred at room temperature overnight (tlc). Next day the reaction mixture was quenched with an aqueous solution of 2N NaOH (5 ml) and extracted with dichloromethane (2 x 25 ml). The organic layer was then washed with water, brine, dried with anhy. magnesium sulphate and concentrated to obtain the crude product. The crude product was purified by silica gel column chromatography using a mixture of chloroform-methanol (1-5%) to obtain pure products 5a-5n (**Table-1**)

RESULTS AND DISCUSSION

Spectral Data

2-(2-Chlorophenyl)-N-((1,3-diphenyl-1H-pyrazol-4-yl)methyl)ethanamine(5a): 7.99 (s, 1H), 7.73-7.75 (m 5H), 7.41-7.47 (m, 5H), 7.31-7.39 (m, 2H), 7.26-7.31(m, 1H), 7.18-7.23 (m, 1H), 3.99 (s, 2H), 3.00 (s, 2H), 2.62 (s, 2H); MS (m/z): 388.2 (M+1); IR (KBr, cm^{-1}): 3412.54, 1635.74, 11647.52, 772.05.

1-(1-((1,3-Diphenyl-1H-pyrazol-4-yl)methyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one(5b): 8.69 (s, 1H), 7.92-7.98 (t, 3H, *J* = 24,12 Hz), 7.76-7.80 (d, 2H, *J* =16Hz), 7.44-7.51 (q, 4H, *J* = 28,8,12Hz), 7.38-7.44 (t, 1H, *J* = 24,12Hz), 7.26-7.31 (t, 1H, *J* = 20,12Hz), 7.18-7.38 (bd, 1H), 7.20-7.29 (m, 3H), 4.32-4.45 (m, 1H), 3.62 (s, 1H), 3.36-3.41 (t, 1H, *J* = 20,12Hz), 3.16-3.24 (bd, 2H), 2.42-2.55 (m, 2H), 2.32-2.42 (t, 1H, *J* = 36,20Hz), 2.18-2.26 (t, 2H, *J* = 32,16Hz); MS (m/z): 479 $(M+H)^{+}$; IR (KBr, cm-1): 1695.74, 1670, 698.41.

2-(4-Fluorophenyl)-N-((1,3-diphenyl-1H-pyrazol-4-yl)methyl)ethana-mine(5c): 8.3 (s, 1H), 7.61-7.65 (d, 2H, *J* = 16Hz), 7.49-7.53 (d, 2H, *J* = 16Hz), 7.35-7.47 (m, 6H), 7.26-7.28 (m, 1H), 6.84-6.97 (m, 4H), 4.15 (s, 2H), 2.98 (m, 2H), 2.81 (m, 2H); MS (m/z): 372.2 (M+1); IR (KBr, cm-1): 1695.74, 1670, 698.41.

4-Phenyl-N-((1,3-diphenyl-1H-pyrazol-4-yl)methyl)butan-2-amine(5d): 8.45 (s, 1H), 7.68-7.72 (d, 2H, *J* = 16Hz), 7.38-7.49 (m, 7H), 7.26-7.30 (d, 1H, *J* = 16Hz), 7.08-7.18 (m, 3H), 6.93-6.96 (d, 2H, *J* = 12Hz), 2.91 (bs, 1H), 2.56 (m, 1H), 2.39 (m, 1H), 2.10 (m, 2H), 1.96 (m, 1H), 1.76 (m, 1H), 1.13 (s, 3H); MS (m/z): 382.2 (M+1); IR (KBr, cm^{-1}): 3030.57, 1657.86, 119.45, 696.14.

2-Morpholino-N-((1,3-diphenyl-1H-pyrazol-4-yl)methyl)ethanamine (5e): 8.37 (s, 1H), 7.71-7.75 (d, 2H, *J* = 16Hz), 7.58-7.62 (d, 2H, *J* = 16Hz), 7.42-7.51 (m, 5H), 7.29-7.34 (t, 1H, *J* = 20,10Hz), 4.32 (s, 2H), 3.63 (m, 4H), 3.16 (m, 2H), 2.92 (m, 2H), 2.36 (m, 4H). MS (m/z): 363.2 (M+1); IR (KBr, cm^{-1}): 3067.57, 1657.21, 1203.20, 698.21.

1-Benzyl-N-((1,3-diphenyl-1H-pyrazol-4-yl)methyl)pyrrolidin-3-amine (5f): 8.40(s, 1H), 7.69-7.73 (d, 2H, *J* = 16Hz), 7.51-7.56 (d, 2H, *J* = 12Hz), 7.38-7.47 (m, 7H), 7.28-7.37 (m, 3H), 4.18 (s, 2H), 4.12 (s, 2H), 3.25-3.58 (m, 4H), 2.89 (m, 1H), 2.08-2.18 (m, 2H); MS (m/z): 409.2 (M+1); IR (KBr, cm^{-1}): 3420.44, 1674.29, 1202.74, 771.98.

N-Methyl-N-((1,3-diphenyl-1H-pyrazol-4-yl)methyl)prop-2-yn-1-amine (5g): 8.45 (s, 1H), 7.73-7.77 (d, 2H, *J* = 16Hz), 7.56-7.60 (d, 2H, *J* = 16Hz), 7.41-7.51 (m, 5H), 7.31-7.36 (t, 1H, *J* = 20,10Hz), 4.38 (s, 2H), 3.80 (s, 2H), 2.68 (s, 3H), 2.34 (s, 1H); MS (m/z): 302.2 (M+1); IR (KBr, cm^{-1}): 3434.86, 1675.30, 1200.54, 770.59.

N-Methyl-N-((1,3-diphenyl-1H-pyrazol-4-yl)methyl)(m-tolyl)methanamine(5h): 8.59 (s, 1H), 7.76-7.81 (d, 2H, *J* = 20Hz), 7.42-7.57 (m, 7H), 7.30-7.36 (t, 1H, *J* = 24, 12Hz), 7.18-7.25 (m, 2H), 7.04-7.11 (m, 2H), 4.46 (m, 1H), 4.26 (m, 2H), 3.80 (m, 1H), 2.44 (s, 3H), 2.24 (s, 3H); MS (m/z): 368.2 $(M+H)^+$. IR (KBr, cm-1): 3436, 2956, 1674, 1504, 1199, 1133, 758.

3-Morpholino-N-((1,3-diphenyl-1H-pyrazol-4-yl)methyl)propan-1-amine (5i): 8.6 (s, 1H), 7.78-7.82 (d, 2H, *J* = 16Hz), 7.62-7.67 (d, 2H, *J* = 20Hz), 7.41-7.52 (m, 5H), 7.30-7.36 (t, 1H, *J* = 24,12Hz), 4.21 (s, 2H), 3.36-3.42 (m, 4H), 3.08-3.13 (m, 2H), 2.53-2.60 (m, 2H), 2.38-2.48 (m, 4H), 1.89-1.96 (m, 2H); MS (m/z): 377.2 $(M+H)^+$. IR (KBr, cm^{-1}): 3407.54, 1641.75, 772.23.

1-((1,3-Diphenyl-1H-pyrazol-4-yl)methyl)piperidin-3-ol(5j): 8.50 (s, 1H), 7.90-7.96 (m, 4H), 7.44-7.54 (m, 4H), 7.30-7.40 (m, 2H), 4.58-4.59 (d, 1H, *J* = 4Hz), 3.38-3.49 (m, 2H), 3.29-3.32 (m, 2H),2.70 (s, 2H), 2.16-2.20 (t, 2H, *J* = 16,8Hz), 1.92-1.94 (m, 3H); MS (m/z): 349.2 (M+1); IR (KBr, cm-1): 3401.54, 1640.75, 765.23.

4-(2-((1,3-Diphenyl-1H-pyrazol-4-yl)methylamino)ethyl)benzene-1-sulfonamide(5k): 8.45 (s, 1H), 7.85-7.87 (d, 4H, *J* = 8Hz), 7.71-7.73 (d, 2H, *J* = 8Hz), 7.49-7.53 (t, 2H, *J* = 16,8Hz), 7.32-7.43 (m, 5H), 7.27-7.30 (d, 3H, *J* = 12,6Hz), 3.77 (s, 2H), 2.84-2.86 (t, 4H, *J* = 8,4Hz); MS (m/z): 433.2 (M+1) IR (KBr, cm^{-1}): 3510, 3416.54, 162675, 768.23.

6-((1,3-Diphenyl-1H-pyrazol-4-yl)methylamino)pyridine-3-carbonitrile(5l): 8.36 (s, 1H), 7.86-7.88 (d, 1H, *J* = 6Hz), 7.72-7.77 (t, 2H, *J* = 15,6Hz), 7.59-7.63 (m, 3H), 7.38-7.49 (m, 4H), 7.26-7.32 (t, 1H, *J* = 18,9Hz), 6.48-6.51 (d, 2H, *J* = 9Hz), 4.66-4.68 (d, 2H, *J* = 6Hz); MS (m/z): 352.2 (M+1).

6-Chloro-N-((1,3-diphenyl-1H-pyrazol-4-yl)methyl)pyridin-3-amine (5m): 7.96 (s, 1H), 7.82-7.83 (d, 1H, *J* = 3Hz), 7.72-7.77 (m, 4H), 7.36-7.49 (m, 5H), 7.27-7.32 (t, 1H, *J* = 15,9Hz), 7.09-7.12 (d, 1H, *J* = 9Hz), 6.87-6.91 (m, 1H), 4.38-4.39 (d, 2H, *J* = 3Hz); MS (m/z): 361.8 (M+1).

6-((1, 3-Diphenyl-1H-pyrazol-4-yl) methyl amino) pyridin-2-ol (5n): 8.58 (s,1H), 7.85-7.88 (d, 2H, *J* = 9Hz), 7.75-7.77 (d, 2H, *J* =6.0Hz), 7.44-7.54 (m, 4H), 7.39-7.41(d, 1H, *J* = 6Hz), 7.31-7.34 (d, 1H, *J* = 9Hz), 7.17-7.22 (t, 1H, *J* = 15,6Hz), 6.39 (s, 1H), 5.54-5.57 (d, 2H, *J* = 9Hz), 4.35-4.37 (d, 2H, *J* = 6Hz); MS (m/z): 343.4 $(M+H)^+$.

CONCLUSIONS

In conclusion, we have reported a facile and convenient synthesis of a series of highly functionalised 4-substituted 1,3-diphenylpyrazole derivatives by the reaction of 1,3-diphenyl-1H-pyrazole-4-carbaldehyde with variously substituted amines following a reductive amination protocol using $ZnCl_2$ and $NaCNBH_3$.

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